Notice of Allowability	Application No.	Applicant(s)	
	10/530,165	ZIEGLER ET AL.	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *11/3/09*.

2. ☒ The allowed claim(s) is/are *1,2,5,6 and 15*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *Herewith* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Maury Audet/
Examiner, Art Unit 1654
Full Sign. Auth. Program

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Andrea Wilkovich, Applicant's Representative, on or about 12/1/2009.

IN THE CLAIMS

In claims 5 and 6, line 4, the term "represents" is deleted, and the term --means-- inserted.

In claim 15, line 1, after the term "claim", the phrase --1 or-- has been inserted.

Claim 7 is cancelled without prejudice.

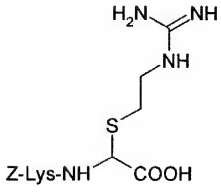
Reasons for Allowance

The following is an examiner's statement of reasons for allowance:

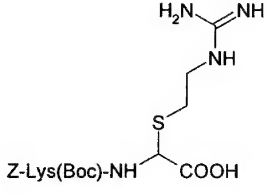
The presently claimed and synthesized substrate formula I - for the compound TAFI conversion to TAFI(a) - comprising an L-Lysine conjugated molecular structure; was not found to be reasonably taught of suggested by the prior art of record. The only result returned on the STN structure search of the claimed compound formula I, as now amended, was Applicant's present application/International continuity chain thereto.

As Applicant's own specification pages 1-3 outlines, the problem being solved was finding a better way to convert TAFI into TAFI(a). Applicant's sites himself the closest prior art of record and where his advancement/improvement over the art is found:

> Measuring the TAFIa concentration in plasma is very useful to evaluate the bleeding and thrombosis risk of patients.
>
> A determination of carboxypeptidases using immunological tests, such as ELISA for example, is possible, but these tests do not consider the activity of TAFI. Functional tests are described, wherein TAFIa acts on synthetic substrates of the R-Arg-COOH or R-Lys-COOH type, thereby releasing "R" (e.g. hippuryl) that can be measured by HPLC or spectrophotometry in the near UV range.
>
> [It is believed Applicant is referring to Greenfield et al.'s work here (e.g. US 7119068 B), which the Examiner uncovered on the hippuryl conjugates].
>
> There is up to now only one chromogenic assay for the measurement of TAFI and TAFIa in plasma on microtiter plates. The dye formation is however too complicated (several steps) and does not give satisfaction. As the absorption is measured at 490
>
> nm, it is not suitable - like the previously described methods - for determination on usual automates where the extinction variations occur at 405 nm.
>
> The thiaarginine derivatives of the following formulas A and B



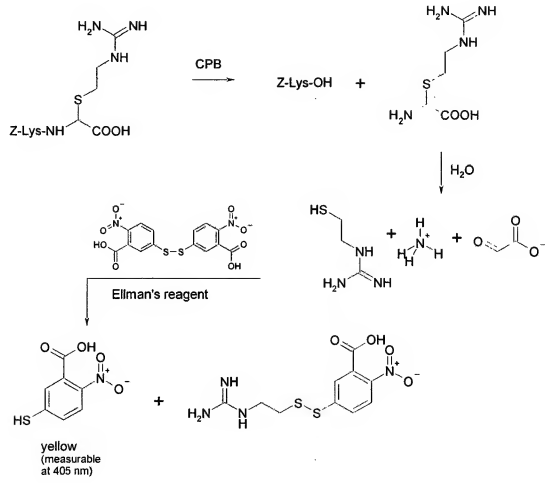
A



B

have been described as substrates for carboxypeptidase B (Bull. Korean. Chem. Soc. 1998, 19(2), 189-193). These compounds are remarkably split off by carboxypeptidase B (CPB), but hardly by TAFIa. Detection of CPB by means of compound A is carried out according to the following Fig. 1.

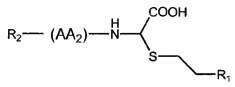
Fig. 1



Surprisingly, this selectivity can be changed in favour of TAFIa already by minor structure variations.

The present invention relates to new TAFIa substrates of the general formula I [as amended and now claimed]:

1. (Currently amended) Compounds of general formula I



wherein

R_1 means a CH_2NH_2 or $NHC(NH)NH_2$ group,

AA_2 means non-substituted or substituted L-lysine, wherein the substituents are common protective groups, and

R_2 means a Bz, Bzl, Ac, Boc, Z, Suc, MeoSuc or Tos group,

provided that the following cases do not occur simultaneously: $R_1 = NHC(NH)NH_2$, $R_2 = Z$ and (AA_2) = non-substituted or Boc-substituted L-lysine,

~~as racemated or as enantiomeric pure isomers,~~

and the salts thereof with mineral or organic acids.

It is noted that the Examiner inquired as to the negative claim limitations in claim 1, to which Applicant's representative thereafter relayed to Examiner that these were not made in view of the art, but rather made because either they were deemed either inferior or non-working combinations. The Examiner noted that search of the art did not reveal these negative limitation combinations.

The International Authority in the National Phase application for the present application, PCT/CH02/00670,.deemed the nearly identical originally claimed subject matter (since narrowed

in this U.S. National Phase) as novel and involving an inventive step; citing only the following two "A" general references of art over the claimed invention:

> TONG ET AL: "Development of substrate forcarboxypeptidase-B by employing thiaarginine peptides" BULLETIN OF THE KOREAN CHEMICAL SOCIETY, Bd. 19, Nr. 2, 1998, Seiten 189-193, XP008018429in der Anmeldung erwAhnt Siehe Seite 189 ("Scheme 1") und Seite192 ("Discussion")
>
> BOFFA ET AL: "Plasma and recombinant thrombin-activable fibrinolysis inhibitor (TAFI) and activated TAFI compared with respect to glycosylation, thrombin/thrombomodulin-dependent activation, thermal stability, and enzymatic properties" JOURNAL OF BIOLOGICAL CHEMISTRY, Bd. 273, Nr. 4, 23. Januar 1998 (1998-01-23), Seiten 2127-2135, XP002183690 ISSN: 0021-9258 Siehe Seite 2131 (GEMSA)

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 12/22/2009

/Maury Audet/
Examiner, Art Unit 1654
Full Sign. Auth. Program